REMARKS

1. Introduction

In this latest response the examiner has maintained all of her prior rejections to the claims at issue, offering no new grounds for rejection, but has only responded in part to the arguments made by Applicant in the last response to her office action. Applicant still contends that the Examiner has failed to properly address or respond to many of applicant's prior arguments, and that the Examiner has continued to cite to what Applicant believes are invalid 35 U.S.C. 103(a) references (Tofovic and Xiao references). As such, combining them with any third reference, U.S. Patent or otherwise, would be insufficient to mount a valid rejection of the claims without first addressing the validity of those references to be cited under said section. Applicant respectfully requests that Examiner review the following arguments despite the finality of this last office action.

2. Rejection of Claims 1-21 under 35 U.S.C. 112, first paragraph.

The rejection of Claims 1-21 was maintained under 35 U.S.C. 112, first paragraph because the specification allegedly fails to enable the prevention of kidney disease for the reasons of record. The Examiner makes two arguments, one, that the claims at hand improperly call out "prevention" when all the examples show "attenuation" of disease. Secondly, the Examiner maintains her prior argument that the specification fails to provide information that would allow one of skill in the art to practice the claimed invention without undue experimentation, citing the 8 factors set forth by *In re Wands*. It is believed that Applicant's earlier response still sufficiently overcomes the second part of the Examiner's argument and is therefore repeated after the new argument below.

In response to the Examiner's new assertion that data showing an attenuation or partial prevention of disease progression does not sufficiently enable a "prevention" claim, Applicants assert that the Examiner is raising the bar for an enablement rejection far higher than the law allows. It is for the F.D.A., not the U.S.P.T.O., to decide when a drug is efficacious or not. Scientists and doctors will not have to embark on a long and undue experimental strategy to decide whether or not the invention at hand works, and when it will work. The Examiner is in many ways acting like a regulatory agent with the unsubstantiated and unreferenced assertions made in this latest office action regarding what would be undue experimentation. The theorized "undue experimentation" simply would not occur in any normal drug regulatory lifecycle.

The Examiner must understand the invention in the context with which it is presented, a drug for the prevention and/or treatment of drug-induced kidney damage. The end users of this invention are physicians, and they are already under a regulatory arm of the government that will ensure they don't use something that hasn't been shown to be effective or safe. What the inventors have shown is that 2-OHE can treat and prevent disease, and nowhere in the law is it required of inventors that to prove one can prevent a disease, one must be able to prevent it one-hundred percent of the time. Were that the case, very few drugs or vaccines would ever receive patent protection, because any person of skill in the medical fields knows that no drug or vaccine or antibody or therapeutic agent of any kind works in every single patient. But the data in the specification (*see below*) clearly shows that this compound works and in a disease relevant model, and that should satisfy all of the required elements for enablement under Section 112.

Applicant refers to paragraph [0049] of the specification which describes a procedure for treating rats with 2-hydroxyestradiol (2-OHE) and leaving some of the rats untreated. Further, paragraph [0055] of the specification discusses some results of rats that were treated with 2-OHE and rats that were not so treated. In particular, paragraph [0055] explains that 2-OHE reduced the PAN-induced mortality rate by 66%. Applicant submits that one of ordinary skill in the art would understand from this statistic that by treating the rats with 2-OHE, such treatment prevented kidney disease and subsequent death in many of the rats. Again to repeat the statement from above, prevention does not have to be absolute, to prevent something means to do any act that will stop an event from occurring. If in the absence of 2-OHE 100% of the PAN treated animals died, and in the presence of 2-OHE there was a 66% decrease in mortality, then by definition 2-OHE prevented the deaths of 66% of the experimental animals. That is both treatment AND prevention.

Further, Applicant submits that paragraph [0058] explains that PAN induces proliferation of glomerular mesangial cells, a proliferation that is a necessary element of kidney disease, and that this effect of PAN is inhibited by 2-OHE. Accordingly, one of ordinary skill in the art would understand from this disclosure that administration of 2-OHE would prevent the aforementioned proliferation and thus prevent the development of kidney disease. Again as stated above, a certain percent of cells were prevented from proliferating, and the examiner is wordsmithing to identify a difference here between what would be seen as treating and preventing. Applicants would ask the Examiner to submit references aside from the Examiner's personal beliefs that show that prevention, in a medical

and clinical setting, is identified as absolute and complete prevention of disease formation or progression.

Similarly, paragraphs [0059] and [0060] disclose that PAN induces glomerular and interstitial infiltration of inflammatory cells, that this infiltration is attenuated by 2-OHE, and they show that PAN expands the extracellular matrix in the glomerular and that this adverse effect of PAN is attenuated by 2-OHE, respectively. Accordingly, Applicant submits that one of ordinary skill in the art would understand from these disclosures that administration of 2-OHE would prevent the aforementioned infiltration of inflammatory cells and the PAN induced expansion of the extracellular matrix in the glomerular, thus preventing kidney disease.

In referring to the 8 factors recited in *In re Wands*, the Examiner argued that the state of the prior art for prevention of nephropathy is underdeveloped. Regardless of the prior art, the Specification of the instant application sufficiently and clearly explains experiments and methods for the prevention of nephropathy as discussed in the foregoing paragraphs of this response.

The Examiner also argues that no working examples are presented in the specification showing how to prevent nephropathies. Applicant respectfully disagrees with the Examiner's argument and submits, as previously explained, that examples of prevention may be found in paragraphs [0058], [0059] and [0060], among others. Furthermore, Applicant directs Examiner's attention to *In re Robins*, 429 F.2d 452, 457 (C.C.P.A. 1970) stating that "representative [samples] are not required by the statute and are not an end in themselves," and to *In re Long*, 368 F.2d 892, 895 (C.C.P.A. 1966) holding that the absence of a working example does not in and of itself compel the conclusion that a specification does not satisfy the requirements of section 112. As such, Applicant submits that Examiner's reliance on the working example argument is misplaced.

Finally, Examiner argues under factor 8 of the test that Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Applicant directs the Examiner's attention to cases that established the groundwork for the *In re Wands* test, such as *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). In that case the inventors appealed a board decision holding undue experimentation would be required to determine which of thousands of possible combinations would work to produce hydroperoxides in their claimed catalytic process. First, the court determined that the claimed process was an "unpredictable" art. The dissent argued that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction*, whether the claimed product will be obtained"

(emphasis in original) *In re Angstadt*, 190 USPQ at 222. The majority rejected this approach, arguing that under the dissent's standard, "all 'experimentation' is 'undue' since the term 'experimentation' implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the Patent Act". *In re Angstadt*, 190 USPQ at 219. The majority continued, "What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended result. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." (emphasis in original), *In re Angstadt*, 190 USPQ at 219. In accordance with the aforementioned legal principles, Applicant submits that upon reading the specification of the instant application, one of ordinary skill in the art would not need to undertake undue experimentation when attempting to practice the instant invention.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1 - 21 under 35 U.S.C. 112, first paragraph.

3. Rejection of Claims under 35 U.S.C. 103(a)

The Examiner has introduced new argumentation as to why, in general, the rejections of claims under 35 U.S.C. 103(a) were proper. Applicant's prior arguments are still deemed responsive and explanatory to the rejection and are included in their entirety below, but in addition to those arguments, Applicant has additional grounds for dispute with these rejections. Without any citation to reference, the Examiner claims that it would be obvious to one of skill in the art that a disclosure that suggests treating "nephropathies" would somehow lead to the treatment of a drug induced kidney disease. This statement suggests the Examiner has not actually read the later Tofovic reference as well as the patent application, both of which suggest why one of skill in the art could not make such a leap of faith and why, in the view of the inventors (and their peers), the later experiments to prove 2-OHE was directly renoprotective were still necessary even in light of their own earlier results.

The abstract cited by the examiner, published by the inventors, merely showed that 2-OHE "attenuates the development of renal disease in genetic nephropathy associated with obesity and the metabolic syndrome." (Tofovic, *J Am Soc Nephrol*, 13:2737, 2002). The inventors believed that further studies were needed to show that 2-OHE "exerts direct renoprotective effects *in vivo*," (Tofovic, 2002), and it is the requirement for these new studies that directly contradicts the

Examiner's uncited and unsupported conclusory statements regarding the obviousness of this invention in light of the inventor's prior published work. Therefore, Applicant contends that Examiner should show at least one reference that supports the conclusion that teachings about attenuation of a genetic disease somehow makes obvious to one of skill in the art claims to preventing drug induced kidney disease. The examiner's line of reasoning here would make any disease treatment or prevention obvious in light of mouse genetic models, and yet the office continually maintains that genetic models are insufficient to enable human therapies because the genetic animals models lack the connection to real life syndrome. It appears that in this instance, the Examiner is saying the exact reverse, that a genetic model somehow makes obvious any other model and any other disease. That simply does not comport with logic or recent practice at the U.S.P.T.O. regarding the validity of genetic animal models.

In regards to the Xiao reference, the Examiner did not even address Applicant's prior arguments made against this reference. As reminded by Applicant in the last response, the Examiner must at least make an effort to address Applicant's arguments. MPEP 707.07(f) clearly states that even when the Examiner finds Applicant's prior arguments to be moot, "the examiner must, however, address any arguments presented by the applicant which are still relevant to any references being applied." Instead, Examiner restated Applicant's argument and then moved on to her discussion of the Allison reference. It is Applicant's contention that neither Tofovic nor Xiao is a valid obviousness rejection, and therefore there is no need to even address Allison in light of either reference.

As such, Applicant's believe all of the Rejections under 35 U.S.C. 103(a) are improper and respectfully request that at this point they be removed and the claims be allowed. Arguments below are responsive to prior arguments made by the Examiner and again repeated in her latest office action, but it is believed that the arguments above are sufficient to explain to the Examiner why the cited references are insufficient to make the invention obvious.

4. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol," *J Am Soc Nephrol* 12: 86A, 2001, for the reasons of record.

Applicant again point out that in order for an Examiner to establish a prima facie case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When an independent claim is deemed nonobvious under 35 U.S.C. 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant respectfully submits that the Examiner has not overcome this burden. Specifically, all of the claims that were rejected by the Examiner recite that the conditions being "prevented" or treated are "drug-induced." Tofovic et al does not teach that the conditions being treated are drug-induced nor does Tofovic et al teach the prevention of such drug-induced conditions. Accordingly, the Examiner has not overcome the aforementioned burden since each and every one of the claim limitations of the instant invention were not taught or suggested by Tofovic et al.

Furthermore, the Examiner has the burden to prove that the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. All of the claims rejected by the Examiner in this office action contemplate preventing various drug-induced conditions. Tofovic et al does not suggest modifying its teachings in order to prevent the conditions mentioned nor does Tofovic et al suggest that its teachings would also be effective in treating or preventing drug-induced conditions. Therefore, Applicant respectfully submits that the Examiner has failed to show that Tofovic et al contains some suggestion or incentive to modify its teachings in order to prevent the conditions or prevent or treat the drug-induced conditions of the instant application.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden. The Examiner stated in the 35 U.S.C. 112, first paragraph rejection beginning on page 2 of this Office Action that this case involves "an unpredictable and undeveloped art." (See (5) on page 4 of the instant Office Action). Therefore, Applicant fails to see how a person of ordinary skill in the art would have a reasonable expectation of success in modifying Tofovic et al to prevent the conditions of the instant application nor treat or prevent the drug-induced conditions of the instant application.

If the field of the instant invention is unpredictable as the Examiner submitted, a skilled artisan would not have a reasonable expectation of success in modifying Tofovic et al to prevent the conditions of the instant application nor would the skilled artisan have a reasonable expectation of success in treating or preventing the drug-induced conditions of the instant application.

In regard to claims 1, 2, 9, 13, 17 and 21, the Examiner argued that it is obvious that the teachings of Tofovic et al would treat the conditions listed in the above claims. However, with the statement made by the Examiner that this case involves "an unpredictable and undeveloped art," absent some motivation or suggestion found in Tofovic et al to modify its teachings, Applicant submits that it would not be obvious that its teachings would treat the conditions listed in the aforementioned claims.

Moreover, the Examiner stated that it is obvious that the teachings of Tofovic et al would "treat" the conditions listed in claims 1, 2, 9, 13, 17 and 21 but the Examiner did not discuss how it is obvious that the teachings of Tofovic et al would prevent the conditions listed in the claims. Since the claims rejected by the Examiner contemplate treating or preventing, the Examiner has not established that each and every one of the claim limitations of the instant invention were taught or suggested by Tofovic et al.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

5. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth," Hypertension, 2001; 37; 645-650, for the reasons of record.

Initially, Applicant respectfully submits that the Examiner mis-characterizes the teachings of Xiao et al. The Xiao et al reference teaches that "...estradiol stimulates endothelial cell-derived nitric oxide (NO) synthesis...," in paragraph 2 on page 645. Furthermore, that same paragraph goes on to explain that, "...decreased NO synthesis...is associated with the pathogenesis of renal diseases..." The end of that paragraph hypothesizes that, "...estradiol may...reduce the rate of progression of renal disease by stimulating NO synthesis..." The conclusion reached by Xiao et al.,

is stated in the final paragraph on page 649 as, "...estradiol may protect against the progression of renal disease by inducing NO synthesis in GECs and inhibiting GMC growth..." It should be noted that all of the aforementioned information relates to estradiol and not estradiol metabolites such as 2-OHE.

Very importantly, Xiao et al., teaches that "[t]reatment with estradiol, but not 2-hydroxyestradiol and 2-methoxyestradiol, induced nitric oxide synthesis. *See* Abstract. Since Xiao et al. concluded that, "...estradiol may protect against the progression of renal disease ***by inducing NO synthesis in GECs and*** inhibiting GMC growth..." it would logically follow that since Xiao et al. teaches that 2-hydroxyestradiol does not induce NO synthesis, it would not protect against the progression of renal disease. (Emphasis added) Accordingly, Applicant submits that Xiao et al. teaches away from the instant application and thus cannot properly be used by the Examiner as support for a 35 U.S.C. 103(a) rejection.

The Examiner has the burden to prove that, among other things, the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. The Examiner argues that one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds. Applicant respectfully disagrees with Examiner's argument. Applicant submits that since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, one of ordinary skill in the art would have no motivation to extend those findings since they teach away from the disclosure of the instant invention.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden either. Since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, Applicant submits that one of ordinary skill in the art would have no expectation of success in protecting against the progression of renal disease *in vivo*, as suggested by the Examiner.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

6. Rejection of Claims 3, 7, 11, 15, 19 and 23 under 35 U.S.C. 103(a)

Claims 3, 7, 11, 15, 19 and 23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Allison (U.S. Pg-Pub 2006/0083778). Specifically, the Examiner argues that Tofovic et al. and Xiao et al. do not teach a controlled release formulation but that Allison teaches a device that is capable of sustained release of the active ingredient. Accordingly, the Examiner argues, it would have been obvious to combine the teachings of Tofovic et al. and Xiao et al. with Allison.

The Examiner submitted that Tofovic et al and Xiao do not teach a controlled release formulation but as Applicant has pointed out in each of the previous 35 U.S.C. 103(a) rejection sections, there are many other things that those references do not teach. Illustratively, Tofovic et al does not teach preventing the conditions of the instant application nor does it teach treating or preventing the drug-induced conditions of the instant application. Further, Xiao actually teaches away from the instant invention because it teaches that 2-hydroxyestradiol does not induce NO synthesis thus it would not protect against the progression of renal disease. Since Xiao teaches away from the instant invention, it cannot properly be used in a 35 U.S.C. 103(a) rejection. Therefore, there is no motivation to combine these references with Allison because both Xiao and Tofovic are incorrectly cited as proper 35 U.S.C. 103(a) prior art.

As previously stated in this Response, the Examiner has the burden to show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Even after combining Tofovic et al and Xiao et al with Allison, the Examiner has not satisfied the aforementioned burden since none of the references suggest or teach preventing the conditions of the instant invention nor do they teach or suggest treating or preventing the drug-induced conditions of the instant invention.

In view of the foregoing, Applicant respectfully submits that all rejections under 35 U.S.C. 112 and 35 U.S.C. 103(a) have been overcome. Accordingly, Applicant believes that Claims 1-24 are in condition for allowance.

Respectfully Submitted,

11-30-07
Date

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